



## Immuno-histochemical profile and demographic pattern of breast cancer patients at a tertiary hospital, Ondo state, south western Nigeria

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### Abstract

**Background:** Breast cancer is still the most common cancer among women. It is the commonest cause of cancer death. The diagnosis of breast cancer is very important. Immunohistochemistry (IHC) is a pathological technique that displays the tissue component by the interaction of target antigens with specific antibodies tagged with a visible label. IHC is an important diagnostic and prognostic tool in breast cancer diagnosis and treatment. It complements the routine histopathology and further helps in accurate tumour and molecular subtype classification of breast cancer.

**Objectives:** The study aims to determine the immunohistochemical classification of carcinomas of the breast based on the estrogen, progesterone, and HER2 neu receptors status, and also to review the socio-demographic factors associated with them in our center.

**Materials and methods:** This was a retrospective cross sectional analysis of 178 histologically confirmed diagnosed breast cancer cases for which estrogen, progesterone, and HER2 status data were available at the Surgery and Oncology outpatient unit of the tertiary hospital in Akure, Ondo state. Relevant bio data, pathology, and immunohistochemical information of all the patients with histologically confirmed breast cancer were extracted from the patients' case files.

**Result:** The mean age was  $49.08 \pm 0.9$  years. The age of the patients ranged from 23 to 78 years. There were 175 (98.3%) females and 3 (1.7%) males. Estrogen, progesterone and HER2 neu positive breast cancers were; 49 (27.5%), 38 (21.3%) and 57 (32%) respectively. Triple negative breast cancer (TNBC) was the most prevalent type, 87 (48.9%), followed by HER2 type 39 (21.9%) and Luminal B 27 (15.2%), while Luminal A 25 (14%) was the least common molecular subtype in our review. There was no significant association between the sociodemographic factors and molecular subtype.

**Conclusions:** The TNBC is the most common type of breast cancer seen in our setting.

Keywords: Immunohistochemistry, Breast, Patient, Tertiary

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#### Introduction

Immuno-histochemistry (IHC) is a pathological technique that displays the tissue component by the interaction of target antigens with specific antibodies tagged with a visible label.<sup>1,2,3</sup> The IHC profile is a special staining process performed on fresh or frozen breast cancer tissue removed during

biopsy.<sup>2</sup> The effective management of breast cancer is very important; thus, it is used to show whether the cancer cells have HER2 receptors and or hormone receptors on their surface.<sup>1</sup> It is useful in defining different prognostic subgroups in relation to treatment received.<sup>3</sup>

IHC has been used to search for specific protein products to observe the unique characteristics of breast cancer, to differentiate breast cancer from cancers of other site origin, to investigate prognostic factors, to obtain information on gene alteration, and to provide predictive factors for effective treatment.<sup>4</sup> IHC helps further provide a differential diagnosis in diagnostically challenging breast lesions. It is a crucial tool in breast cancer diagnosis and classification. It helps to identify subtypes, predict treatment response, and assess prognosis. The subtypes include Luminal A, Luminal B, HER2 overexpression, and triple negative. The last two usually give a poorer prognosis.<sup>5,6</sup>

The role of Immunohistochemistry (IHC) is really outstanding in the diagnosis and management of breast diseases. The more available antibodies, improved retrieval of antigens, and increased knowledge on the biology of the disease have made the use of immunohistochemistry more relevant in solving issues on the diagnosis and management of Breast cancer.<sup>3</sup> Breast cancer is no longer regarded as a single entity, and morphological evaluation alone cannot predict the behavior of breast cancer; hence, the use of IHC to further characterize breast cancer globally.<sup>3</sup>

Molecular phenotyping using the IHC procedure is cheaper and easier to set up for molecular sub-classification of breast cancer.<sup>6</sup>

In Nigeria, Breast cancer is the most common cancer in women, and it is currently a major public health problem.<sup>7,8</sup> It is the commonest cause of cancer death among women globally. Over 1.38 million breast cancer cases are diagnosed worldwide, representing 10.9% of all cancers.<sup>3</sup> In sub-Saharan Africa, the recent estimates show that the overall incidence rate was 24 per 100,000 persons/ year in the hospital and 22.4 per 100,000 in the community.<sup>14,15</sup> The peak age is between 35 years and 49 years among African women, 15 years earlier than European and North American women. The mortality rate among sub-Saharan women is higher as tumours are more aggressive and the time from

onset of disease to diagnosis is short.<sup>4,11</sup>

Breast cancer is a heterogeneous disease with a wide spectrum of pathological, clinical, and molecular features. The three most common immunohistochemical markers commonly used in diagnostic use are estrogen receptor (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2 neu).<sup>12,13</sup> these markers determine which tumours are likely to respond to hormonal or targeted therapy. There are several studies that have shown that the luminal subtype could be further separated into luminal A and luminal B. This is reflected in the differences in their prognosis. The overall survival is usually favourable for luminal A and least for triple-negative breast cancer.<sup>11,13,14</sup>

The use of immunohistochemistry classification is regarded as the gold standard, but the use of gene expression profiling is limited to clinical or research purposes.<sup>12,13,15</sup>

In recent times, researchers have used IHC to classify tumours basically as Luminal and non-luminal tumours. This is defined as tumours that express either ER or PR, and those that do not.<sup>14,15,16</sup>

This classification is further subdivided according to HER2 expression status. Luminal A tumours have high expression of ER-related genes and lower proliferating genes than the luminal B tumours. While the non-luminal tumours are ER and PR negative. The ones that do not express ER, PR, or HER2 are the triple negative phenotype, also called basal-like tumours.<sup>17,18,19</sup>

The influence of age at diagnosis of breast cancer upon the prognosis of patients with different IHC-defined subtypes is still incompletely defined. The IHC profiles can vary with age, particularly in breast cancer, where the hormone receptor status and HER2 expression may change with age. Age at diagnosis has been reported as an independent prognostic factor for breast cancer in several studies.<sup>4,20,21</sup>

The basal-like or triple-negative breast cancer (TNBC), characterized by negative ER, PR, and HER2 expression, is more prevalent in Africans and African Americans than in white women. Additionally, some other studies have found differences in breast cancer subtypes between different ethnic groups within Nigeria.<sup>22,23,24</sup>

This study aims to evaluate the

immunohistochemistry profile and the associated demographic factors of breast cancer in Ondo State, Nigeria.

### Material and methods

This was a retrospective review of 178 histologically confirmed breast cancer cases for which bio data on the immunohistochemical data were available in the Pathology, Surgical, and Oncology unit of the University of Medical Sciences Teaching Hospital, Akure, Ondo State, Nigeria, from March 2015 to April 2023.

The University of Medical Sciences teaching hospital is a centrally situated teaching hospital in the capital city of Ondo state, offering tertiary specialist care as well as referral services spanning all the geographical locations across the State. It has a bed capacity of over 400 beds. It serves primarily the indigenes of Ondo State as well as the border towns of the neighboring Ekiti, Osun, Edo, and Ogun States.

### Data Collection

For each case of cancer of the breast, the socio-demographic data extracted were: age, laterality, stage at diagnosis, level of education, location, religion, histological type, parity, marital status, treatment offered, outcomes, and molecular subtypes. Breast carcinomas with missing immunohistochemical profiles of ER, PR, and HER2 in the archives were excluded from the study. Based on the standard immunostaining profile, the molecular phenotypes were classified as Luminal A cancers (ER+/PR+, HER2- or ER-/PR+, HER2- and ER+/PR-, HER2-), Luminal B cancers (ER+/PR+, HER2+ or ER+/PR-, HER2+ or ER-/PR+, HER2+), triple negative breast cancer (ER-/PR-, HER2-) and HER2 enriched cancers (ER-/PR-, HER2+).

### Data Analysis

The data was analyzed using the SPSS version 27 statistical package for Windows. Descriptive and inferential statistics (chi-square) were used. Mean and standard deviation were determined for quantitative normally distributed data, frequency and percentage were used to describe categorical data and chi square test was used to determine the association between categorical variables. Level of statistical significance was set at  $p < 0.05$ . The results

were presented using tables and charts.

**Ethics considerations:** Institutional Ethical Approval was obtained from the State Ministry of Health Research and Ethical Committee (OSHREC), (HREC/02/01/2025). Confidentiality was ensured by not writing the names of patients on proforma by the Helsinki declaration.

### Results

#### Breast data, age, sex and IHC distribution

Nine hundred and twenty surgical breast lesions were diagnosed during the period of study. Primary breast cancers constituted 42% (384/920) of all the breast lesions. Immunohistochemical data (ER, PR, HER2) were available for 178 (46.4%) of these carcinomas. The age of the patients ranged from 23 to 78 years, and the mean age was  $49.08 \pm 0.9$  years at diagnosis as shown in Fig. 1. The median age was 49 years, and the modal age was 47 years. Most of the breast cancers were located on the right 106(59.6%), 65(36.5%) were located on the left, and 4(2.2%) were bilateral.

About 59% of patients were aged  $\leq 50$  years, and 41% were greater than 50 years of age. There were 175 (98.3%) females and 3 (1.7%) males. Most of the patients were Christians, 151(84.8%), and 27(15.2%) were Muslims. Triple negative breast cancer 87(48.9%) accounted for the highest number of IHC types, followed by HER2-enriched type 39(21.9%), Luminal B 27(15.2%), while Luminal A 25(14%) was the least, as shown in Table 1.

Table 1: Sociodemographic Characteristics of Respondents

Variables	Frequency(n)	Percent (%)
<b>Age group (years)</b>		
20 – 29	7	3.9
30 – 39	33	18.5
40 – 49	57	3.2
50 – 59	45	25.2
60 – 69	26	14.6
70 – 79	10	5.6
<b>Marital status</b>		
Married	132	74.2
Separated	20	11.3
Single	10	5.6
Widow	16	8.9
<b>Level of Education</b>		
Tertiary	78	43.8
Secondary	80	44.9
Primary	14	7.9
None	6	3.4
<b>Parity</b>		
0	8	4.5
1	8	4.5
2	30	16.9
3	73	41
4	45	25.3
5	12	6.7
$\geq 5$	2	1.1

Table 2: Frequency distribution of IHC receptors (ER, PR, HER2) and molecular Classification

Variable	Frequency (n 178)	Percent (%)
<b>ER</b>		
ER negative	129	72.5
ER positive	49	27.5
<b>PR</b>		
PR negative	140	78.7
PR positive	38	21.3
<b>HER 2</b>		
HER 2 negative	121	68
HER 2 positive	57	32
<b>Molecular classification</b>		
HER 2 enriched	39	21.9
Luminal A	25	14
Luminal B	27	15.2
TNBC	87	48.9

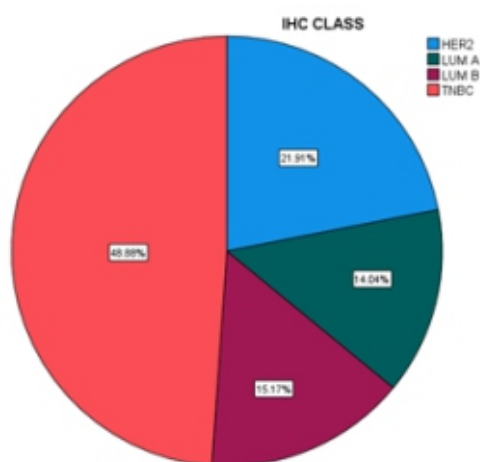


Fig. 1: IHC classification

**Histopathological characterization and staging**

The commonest histopathological pattern was invasive ductal carcinoma 168 (94.4%), followed by invasive lobular carcinoma 7(4%), carcinoma in situ 2(1.1%), while medullary carcinoma 1(0.6%) was the least. In the study, the staging of the breast cancer revealed that a large number 77(43.3%), presented in stage 4, 73((41%) presented in stage 3, 25(14%) in stage 2, 1(0,6%) in stage 1, and 2(1.1%) in stage 0.

Table 3: Histopathology and Staging distribution

Variable	Frequency (n=178)	Percent (%)
<b>Histopathology</b>		
Invasive ductal carcinoma	168	94.3
Invasive lobular carcinoma	7	4
Carcinoma in-situ	2	1.1
Medullary	1	0.6
<b>Stage</b>		
0	2	1.1
1	1	0.6
2	25	14
3	73	41
4	77	43.3

**Treatment distribution and outcome**

Table 3 shows the treatment distribution and outcome in this study. Analysis of the treatment offered revealed that majority of the patients did not have mastectomy done 91(51.1%), while 87(48.5%) had mastectomy at one point in time. Chemotherapy was administered to most of the patients 173(97.2%) and only 5(2.8%) did not receive chemotherapy. A total of 113 (63.5%) had radiotherapy and only 44(24.7%) had hormonal therapy. The treatment outcome analysis showed that most of the patients were still on treatment 62 (34.8%), followed by the patients that were late 45(25.4%), those that were lost to follow were 36(20.2%) and the least were patients that defaulted from treatment 4(2.2%) as shown in Fig.3.

Table 4: Treatment distribution of Patients

Variable	Frequency (n 178)	Percent (%)
<b>Surgery</b>		
Yes	87	48.9
No	91	51.1
<b>Chemotherapy</b>		
Yes	173	97.2
No	5	2.8
<b>Radiotherapy</b>		
Yes	65	36.5
No	113	63.5
<b>Hormonal therapy</b>		
Yes	44	24.7
No	134	75.3

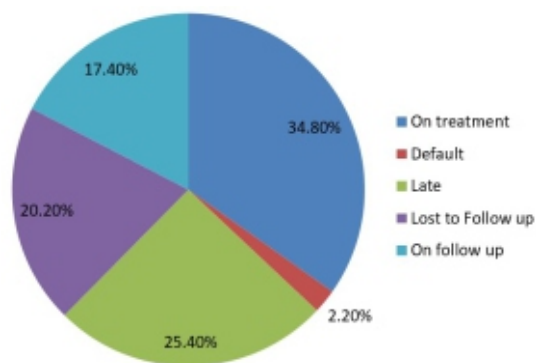


Fig. 2: Treatment outcome distribution.

**Association between age, parity and IHC pattern**

Table 5 shows the association between age and the IHC type. There was no significant relationship between age and the IHC type, not statistically significant. p= 0.703. The distribution of IHC types does not vary significantly across age groups in this dataset.

Also there is no statistically significant association between IHC type and parity p = 0.409

Table 5 Association between selected variables and IHC pattern among patients

Variables	IHC TYPE				Statistical test and p value
	LUMA	LUM B	TNBC	HER2 TYPE	
Agegrp(yrs)					$\chi^2 = 1.411$ p = 0.703
20-29	3	1	2	1	
30-39	5	5	18	5	
40-49	4	13	20	20	
50-59	4	3	29	6	
60-69	7	2	16	4	
70-79	2	3	2	3	
Parity					$\chi^2 = 21.838$ p = 0.409
0	2	3	3	0	
1	4	2	1	1	
2	4	6	10	5	
3	4	8	45	30	
4	7	3	24	2	
5	4	5	2	1	
>5	0	0	2	0	

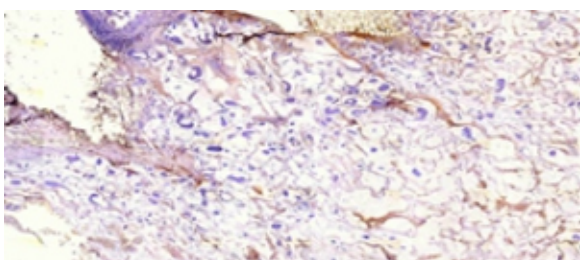


Fig. 5: Photomicrograph of breast carcinoma immunostained negatively for estrogen receptor showing complete absence of nuclear staining x 40

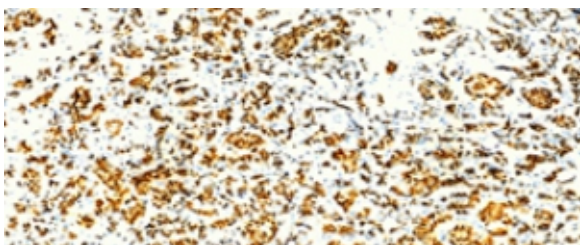


Fig. 6: Photomicrograph of breast carcinoma immunostained positively for estrogen receptor showing strong diffuse nuclear staining x 40

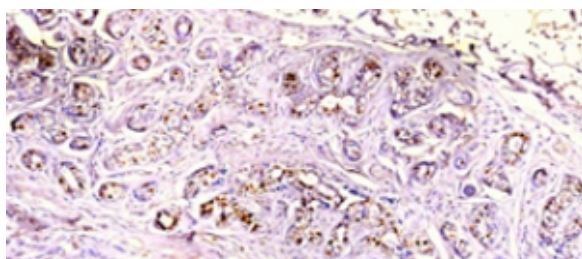


Fig. 7: Photomicrograph of breast carcinoma immunostained positively for progesterone receptor showing strong diffuse nuclear staining x 40

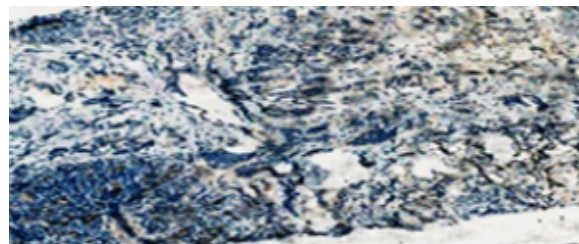


Fig. 8: Photomicrograph of breast carcinoma immunostained negatively for progesterone receptor showing complete absence of nuclear staining x 40

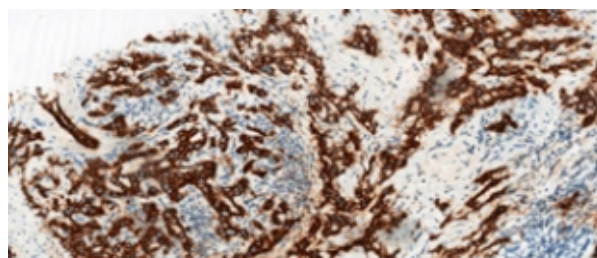


Fig 9: Photomicrograph of immunostained breast carcinoma Her2: 3+ strongly diffuse membrane staining. x 40

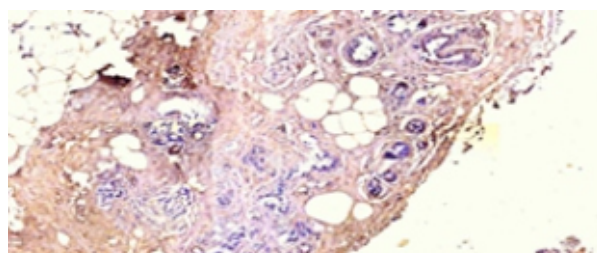


Fig. 10: Photomicrograph of immunostained breast carcinoma Her2 negative showing absence of membrane staining x 40

**Discussion**

The mean age at diagnosis is 49.08 years; the age range is 23 - 78 years, with 59% and 49% ≤ 50 years and greater than 50 years, respectively. The mean age at presentation in our current study is in agreement with studies from Maiduguri (46.7 years) and Abuja (47.3 years)<sup>13,15</sup> but lower compared to that from Togo (52.05 years)<sup>26,27</sup> and the UK (55years)<sup>28</sup>, while the age range is quite similar to studies from Togo. This affirms the fact that breast cancer occurs more in the middle-aged group in our setting.

Immunohistochemistry (IHC) classification of both ER, PR, and HER2 status provides basic information of a histologically confirmed breast carcinoma. In this study, the IHC was performed in only 46.4% of breast cancer diagnoses. This is higher compared to the study done in Guinea (38.2%), Sudan (40.2%), and Togo (37.5%).<sup>24,25,26</sup> The reason may be due to the unavailability and high cost of receptor status testing in our country, and access to IHC is quite limited in most countries of the Sub-Saharan Africa.

In our study, triple-negative breast cancer (TNBC) 87 (48.9%) was the most common molecular subtype of breast carcinoma seen. This is quite higher as compared to the studies done in Nnewi, 40.7%, Ghana, 39%, Abuja, 42% and Togo, 37.6%.<sup>5,26,27,29</sup> In advanced countries such as the United Kingdom and America, TNBC was quite lower 25% and 15% respectively.<sup>28,30</sup> This variation may be because most of the women in Sub-Saharan African countries present with the aggressive form of the disease, which also correlates with the triple negative breast cancer subtype. HER2-enriched type accounted for 21.9% in our study; this was quite higher compared to studies from Abuja and Togo with 12.5% and 7.7% respectively. Luminal B type was 27 (15.2%), and the least common was Luminal A, 25(14%), which was lower than in studies from Maiduguri, Lagos, Ile-Ife, and Benin.<sup>3,31,32,33</sup> Luminal B subtype was 14.7%, 13.2% and 12.9% in Abuja, Maiduguri, and Calabar, respectively, but lower in Kano and Nnewi, 6% and 4%. Luminal A breast cancer subtype was found to be higher in studies from Ibadan, 79.6%, Bayelsa, 54%, Ethiopia, 40% and Guinea, 34.5%.<sup>25,28,29,30</sup> This trend may be due to more hormone-negative receptor breast cancer seen in our environment.

The IHC pattern in our study showed that hormone receptor-positive breast carcinomas were less prevalent than their negative counterpart. This is similar to studies from Jos and Ethiopia<sup>34,35</sup> but, higher in studies from Asia, the Ivory Coast, Abuja, and Togo.<sup>6,26,36,37</sup> This may be because most of the breast carcinomas seen in Sub-Saharan Africa are quite aggressive in nature with negative hormone receptor status. The ER, PR status in our study revealed ER+ PR+ as 27.5%, 21.3% while ER - PR- was 72.5% and 78.7% respectively. This was lower than studies from Abuja (56.6%, 61%), Togo

(54.7%, 41%), and Maiduguri (45.2%, 32.2%).<sup>6, 26</sup> The commonest histopathological variant in our study was invasive ductal carcinoma, 94.4%. This was quite similar to Abuja, 94.12%, lower than the study from Togo, 95.75%, and higher compared to the study from Maiduguri, 88.2%. This is likely due to the varied small sample sizes of the various hospital-based studies across such cities and countries.<sup>3</sup>

The socio-demographic and other clinical factors analyzed in our study ranged from sex distribution, religion, level of education, parity, stage at presentation, the treatment offered, and outcome of the treatment. In our study, most of the patients were Christians 84.8%% and were married 74.2%. This is quite lower than a study done in western Nigeria, 90.5% and 85,7% respectively.<sup>38</sup> The laterality of the disease showed that most of the breast cancers were located in the right breast 59.6%, than on the left 36.5% while it was bilateral in 2.2%. This value is quite higher compared to a similar study in Akure, Ondo state which reported 50%, 44.5%, and 1.2% respectively.<sup>38</sup>

Comparing the parity of the patients, our study revealed that 41% of the patients had 3 children and 5.1% were nulliparous, which is quite similar to a study in South-west Nigeria with 39% and 5% respectively.<sup>38</sup> This was contrary to a study in Baghdad, where 41.6% of the women were nulliparous,<sup>39</sup> though several studies have noted that nulliparity is an associated risk factor for breast cancer,<sup>39,40,41,42</sup> but our study showed that most of the women were multiparous; this may be due to cultural disposition and early marriages. Invariably, this study demonstrated interesting facts about the molecular subtypes of breast cancer and demographic features associated with the disease.

### Limitations

1. Even for the histologically confirmed breast cancer cases, not all have had IHC done, and this scenario has thus affected the representativeness of our sample.
2. Larger studies from population-based samples are needed to help monitor breast cancer control programs.
3. Also, the relative inability to explore and further characterize the IHC in our environment, has made it challenging to enable a more distinct

molecular classification of African IHC breast cancer type and to further have a more targeted therapy for effective cancer care.

### Conclusion

In our study, triple-negative breast cancer (TNBC) was the most common molecular subtype of breast cancer seen, while the least common was the luminal A subtype. Most of the patients presented at the later stage of the disease, and these results are expected to have important clinical implications and review for treatment, prognosis, and quality of life of breast cancer cases in our environment. This study emphasizes the need for a more comprehensive histopathological evaluation with a corresponding immunohistochemical review of breast cancer diagnosis in our routine clinical practice to offer the best breast cancer management.

### Declarations

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### Authors' contributions:

Ndidi Okunnuga – Conceived the study and also was involved in the design and coordination as well as helped to draft the manuscript. She also read and approved the final manuscript.

The co-authors; Bamidele Alegbeleye, Peter Ologunagba, Adetokunbo Okunnuga, Adewale Ayadi and Olorunwa Kolawole all participated in its design, manuscript draft, also read and accepted the final manuscripts.

**Conflict of interest:** The authors have no conflict of interest relevant to this article to disclose.

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